REMARKS

Status of the Claims

Claims 1 and 7 are pending. Claims 1 and 7 are rejected. Claim 1 is amended herein. Claims 2-6 and 8-22 are canceled. No new matter has been added.

Claim amendments

The preamble of claim 1 is amended to recite method of increasing the probability of remission after treatment in a human having a solid cancerous tumor greater than 1 mm in size. Also, step (c) of claim 1 was amended to clarify that the selected dose is an amount effective to bind a sufficient plurality of said targeted sites on tumor cells and that a minimum of two atoms of bismuth-213 delivers at least one alpha particle to each targeted tumor cell upon antibody binding. In addition, step (d) of claim 1 was amended to recite that each repetition kills an additional layer of tumor cells thereby sequentially reducing the size of the solid tumor such that the tumor growth probability approaches one, thereby increasing the probability of remission in the individual (pg. 19, ll. 6 to pg. 20, ll. 12). No new matter was added in this amendment.

The 35 U.S.C. §112, first paragraph, rejection

Claims 1 and 7 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to make

and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The Examiner states that the specification, while being enabling for a method for sequentially reducing the size of a solid cancer greater than 1 mm in sized, does not reasonably provide enablement for a method that sequentially reduces the tumor until tumor growth cannot recur. The Examiner states that one cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the treated subject would not have cancer recurrence.

Applicants have amended the claims as shown supra. The scope of amended claim 1 is to sequentially reduce the size of the tumor using a high specific activity bismuth-213/tumor specific antibody construct. Sequential removal of layers of tumor cells increase the tumor control probability, and thereby the probability of remission, in individuals having a solid tumor greater than 1 mm. As amended, the scope of claim 1 does not encompass non-recurrence of tumor growth, but rather an increase in probability of remission. It is a probability of response in a population of tumor cells or in an individual. Predicting whether an individual will respond to the treatment with 100 certainty does not fall within the scope of the claims. In the art no one can predict with 100% certainty whether an individual will respond to any drug.

The specification discloses the necessity for high specific activity constructs to enable therapeutic results and the necessity for even higher specific activity to approach or achieve a tumor control probability (TCP) of one

in the cancer. The specification teaches how the tumor control probability can be determined for a given amount of tumor cell killing. The probability of remission increases as the tumor control probability approaches one. However, the specification also teaches that to sequentially reduce tumor size, i.e., the number of cancer or tumors cells, using alpha emitters to effectively approach a tumor control probability of one requires designing, in this instance, a bismuth-213 labeled antibody construct which must take into consideration at least the high specific activity, the half-life, the type of antibody, the number of target sites, etc. to effectively kill sequential layers of tumor cells in the solid tumor.

The Examiner states that it is well known in the art that cancer antigens are heterogeneous and that the amount or level of antigens expressed on cancer cell surface could vary significantly in different individual cancer cells. The Examiner states that in view of this and of the requirement to achieve reliable cell killing depends on the number of receptor targets on the target cell, one cannot predict that the treated subject would not have cancer recurrence.

Applicants have amended claim 1 as shown supra. The high specific activity of the Bi-213/antibody construct is detemined, *inter alia*, from the number of antigen binding sites commonly associated with the particular tumor cell. The requirement is not that every cell comprising the tumor must express the antigen in these numbers, it is a guideline in determining a specific activity high enough to kill an outer layer of tumor cells when an effective dose of the construct is administered. The claim recites that the dose is enough to provide an amount of antibody to bind to a sufficient plurality of targeted sites on an outer

layer of tumor cells so that, upon binding, a minimum of two atoms of bismuth-213 delivers at least one alpha particle to each tumor cell having an antibody bound thereto. This is demonstrably sufficient to destroy at least one layer of tumor cells.

Particularly, the specification demonstrated that a single dose of bismuth-213 has eliminated 5 to 6 layers of cells in a spheroid model, leaving behind a previously unexposed "core" of cells that can then be targeted by a subsequent administration (pg. 11, ll. 3-8; pg. 39, ll. 5-9; Fig. 2). Although Applicants have amended the preamble and claim steps, as discussed, the specification certainly demonstrates that a Bi-213/antibody construct targets and binds a sufficient number of antigen binding sites to repeatedly or sequentially kill tumor cells in exposed outer layers of the solid tumor. Thus, even given the heterogeneous nature of tumor cells in a tumor, a suitable dose of a high specific activity Bi-213 labeled antibody is effective to sequentially remove layers of tumor cells and thereby increase the probability of remission.

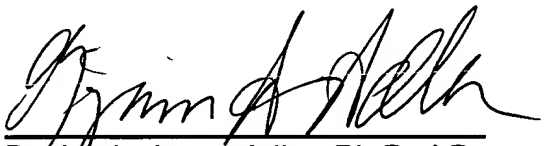
Claim 7 depends from amended claim 1 and further limits the dose of Bi-213 antibody construct. Since one of ordinary skill in the art would be able to make and to use the invention commensurate in scope with amended claim 1, so would dependent claim 7 be enabled.

Accordingly, in view of the claim amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §112, first paragraph, be withdrawn.

Applicants submit that claims 1 and 7, as presented herein, are in condition for allowance. Accordingly, Applicants request that claims 1 and 7 be passed to issuance. This is intended to be a complete response to the Office Action, mailed February 14, 200,. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants enclose a Petition for a Three Month Extension of Time. Please charge the $510 petition fee to the credit card identified on the enclosed Form PTO-2038. In the absence of Form PTO-2038, please debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: August 14, 2006



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